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Is Childhood Vaccination Associated With Asthma? A Meta-analysis of Observational Studies

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ABSTRACT

BACKGROUND. The possible link between immunization and atopic diseases has been under intense debate in the last decade.

OBJECTIVE. The aim of this study was to systematically review the available evidence on the association of whole-cell pertussis and BCG vaccination with the risk of asthma in childhood and adolescence.

METHODS. The major medical electronic databases (Medline, National Library of Medicine Gateway, and Cochrane Library) were searched, and reference lists of the relevant publications were reviewed for relevant birth-cohort studies and randomized, controlled trials from 1966 to March 2006. Only studies that directly compared vaccinated and unvaccinated children, validated vaccination status by medical charts, and used preset criteria to define asthma were included. Data were abstracted by using a standardized protocol and computerized report form. Results were analyzed by applying a fixed-effect or random-effect model, according to the heterogeneity of the studies. Sensitivity analyses by scoring criteria were performed.

RESULTS. Seven studies of pertussis vaccination (with a total of 186 663 patients) and 5 studies of BCG vaccination (with a total of 41 479 patients) met our inclusion criteria. No statistically significant association was detected between either whole-cell pertussis or BCG vaccination and incidence rates of asthma during childhood and adolescence. This lack of a significant association proved to be robust on sensitivity analyses for BCG but not for pertussis vaccine.

CONCLUSIONS. Currently available data, based on observational studies, do not support an association, provocative or protective, between receipt of the BCG or whole-cell pertussis vaccine and risk of asthma in childhood and adolescence.

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Key Words

vaccination, asthma, meta-analysis

Abbreviations

DTP—diphtheria-tetanus-pertussis

BCG—bacille Calmette-Guérin

OR—odds ratio

CI—confidence interval

Th—T helper

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IN THE PAST 3 decades we have witnessed a dramatic increase in the prevalence of asthma and allergic disease worldwide, most notably in countries with a Western lifestyle.¹ Most cases of asthma first appear in childhood, with 80% to 90% of patients diagnosed by 6 years of age.² Gene-environment interactions are critical to the pathogenesis of allergic disorders such as asthma, and the susceptibility to asthma was shown to be increased by conditions that are present early in life, including family history of asthma or other manifestations of atopy, male gender, low birth weight, preterm birth, young maternal age, early cessation of breastfeeding, and parental smoking.³

The association between vaccination uptake and the risk of atopic diseases was first proposed by Odent et al⁴ in a letter published in the *Journal of the American Medical Association* in 1994. Thereafter, several studies have suggested either a provocative or protective effect of immunization depending on the specific vaccine, the target population, and the age at which the vaccine was administered.⁵⁻⁷ Whole-cell pertussis (as a component of diphtheria-tetanus-pertussis [DTP] vaccines) and bacille Calmette-Guérin (BCG) vaccines are among the most extensively studied in regard to their suggested effect on risk of atopic diseases.

More-recent systematic reviews have failed to support these findings (although no formal meta-analyses have been conducted, partly because of the heterogeneity of the studies^{8,9}), including 2 independent population-based studies published in 2005 that reported a possible atopy-protective effect of immunization.^{10,11} It is important that researchers clarify this issue, because unless refuted, the perception that immunization causes asthma may become a significant determinant of parents' attitudes toward routine vaccination of their children.¹²

The aim of this study was to systematically review the literature on the possible association of whole-cell pertussis and BCG vaccination in the first year of life with the incidence of asthma in childhood and adolescence and to perform a meta-analysis of the relevant studies.

MATERIALS AND METHODS

Search Strategy

A search of the major medical electronic databases (National Library of Medicine Gateway, Medline, and Cochrane Library) was conducted for articles published from January 1966 to March 2006 that contained the keywords "vaccine," "BCG," "pertussis," "allergy," "atopy," "wheezing," and "asthma," alone or in combination. Thesaurus and free-text terms (including synonyms) were used in various combinations depending on the requirements of the particular database. In addition, we used the "related articles" function in PubMed, as well as the "articles citing this study" function in

online journals. We also manually searched the reference lists in all identified publications and recent systematic reviews.

Selection of Articles

The abstracts of all articles identified were reviewed, and 71 relevant original scientific studies were read in full. In the preliminary assessment, we excluded cross-sectional studies and studies that did not directly compare subjects who were vaccinated with BCG or DTP/whole-cell pertussis vaccine ("pertussis vaccine") with unvaccinated subjects. We also excluded studies in which asthma status in childhood or early adolescence (up to 16 years old) did not serve as an independent outcome measure. When several studies pertained to the same cohort, the study with the longest follow-up period was selected for inclusion. The 24 remaining articles for final assessment^{4,10,11,13-33} were independently reviewed and scored by 2 of us (Drs Balicer and Grotto).

Data Abstraction and Validity Assessment

Two of us (Drs Balicer and Grotto) abstracted information from each of the 24 selected studies. All data were abstracted by using a standardized protocol and computerized report form.

Among these 24 articles, we selected only those that met our preset criteria: randomized, controlled trial or birth-cohort study, either prospective or retrospective (including those with a nested case-control design); assessment of vaccination status using the medical charts; asthma/bronchial hyperresponsiveness diagnosed on the basis of a validated questionnaire or the medical charts; and asthma defined as (1) at least 1 reported or recorded episode of wheezing or bronchial obstruction, (2) reported coughing in the morning or during the day or evening in the autumn and winter and coughing daily for ~3 months/year, (3) physician-diagnosed asthma or obstructive bronchitis, or (4) ever-recorded medications for asthma or wheezing. Thirteen articles were eliminated on this basis, which left 11 studies for analysis.

Quantitative Data Synthesis

All analyses were performed separately for pertussis and BCG vaccination. The overall odds ratios (ORs) and 95% confidence intervals (CIs) for asthma were calculated by using the OR and variance of each study. The overall measure was summarized by the precision-based estimates described by Fleiss³⁴ and Kleinbaum et al,³⁵ which assume a homogeneity of effect between studies (fixed-effect model), and the method of DerSimonian and Laird,³⁶ which factors in both within-study variance and heterogeneity between studies (random-effect model). Heterogeneity of the ORs across n studies was tested with the following formula: χ^2 heterogeneity = $\frac{\sum w_i M_i^2 - (\sum w_i M_i)^2 / \sum w_i}{\sum w_i}$, where M_i is an individual measure of association (logarithm of the OR), and w_i is a weighting

factor equal to the reciprocal of the squared SE (determined by the upper and lower limits of the 95% CI) of the individual measure.³⁴ Statistical significance was evaluated with $n - 1$ degrees of freedom.

Quality Ranking and Sensitivity Analysis

The studies included in the final assessment were appraised and ranked for methodologic quality within the process of the sensitivity analyses. Criteria concerning the study design merited 1 point for each of the following: group randomization, retrieval of outcome data from medical charts, a relatively large unvaccinated group (>25% of the study population), and studies that performed and reported the results of a multivariate analysis that accounted for gender, family history of asthma and/or allergy, socioeconomic status, parental smoking, low birth weight, young maternal age, and prolonged breastfeeding (1 point for each factor adjusted for). For cases in which a relevant multivariate analysis was not performed or its results were not available, univariate analysis results were used in the meta-analysis and no quality score was granted for adjustment criteria. Studies were scored and ranked according to the sum of points (range: 0–11). In case of equal scores, the study that scored higher in the first 3 above-mentioned study-design criteria was ranked higher. Disagreements or uncertainties were resolved by discussion among all the investigators.

We performed sensitivity analyses in which we excluded studies from the pool to examine their effect on the pooled estimate and CIs.³⁷ First, we removed each one of the studies, and then we excluded the study with the lowest-quality score and then 2 studies with the lowest-quality scores. We also recalculated the pooled estimates, including only studies in which unvaccinated subjects comprised at least 25% of the total cohort, thereby adjusting for several potential bias factors. All computations were performed by using PEPI 3 (USD, Inc, Stone Mountain, GA) for epidemiologic analysis.

RESULTS

Trial Flow

After screening >2000 potentially relevant citations, 71 reports of relevant original data were identified and read completely, of which 24 met the preliminary inclusion criteria, as detailed above. Thirteen of these studies were ultimately excluded for the reasons detailed in Table 1.

Study Characteristics

Seven studies of the pertussis vaccine (with a total of 186 663 patients) and 5 studies of the BCG vaccine (with a total of 41 479 patients) were included in the meta-analysis.^{13–23}

One study assessed both pertussis and BCG vaccines and was included in both analyses.¹⁵ The main features of these studies, organized by quality score, are shown in Table 2.

Quantitative Data Synthesis and Sensitivity Analyses

BCG Vaccination and Asthma

Figure 1 presents the ORs and 95% CIs of the 5 studies that investigated the association between BCG vaccination and asthma. Two of them,^{19–21} including a relatively large-scale study that yielded statistical results of borderline significance, reported a protective association.¹⁹ The studies were not found to be heterogeneous ($\chi^2 = 4.89$; $P = .299$); therefore, we used the OR that was calculated according to the fixed-effect model as the overall estimate. The OR was 0.98 (95% CI: 0.88–1.08), which indicates that BCG vaccination had no overall effect on the occurrence of asthma in childhood or adolescence.

Because the heterogeneity did not reach statistical significance after exclusion of each of the studies, we continued to use the fixed-effect model for our sensitivity analyses (Table 3). The exclusion of each study yielded similar results, with an OR of 0.89 to 1.06 and a CI that overlapped 1.0 in all analyses. Table 3 summarizes these results, as well as 2 additional sensitivity

TABLE 1 Selected Studies Not Included in the Meta-analysis

Trial	Year	Country	Vaccine	Main Reason for Exclusion
Odent et al ¹⁴	1994	United Kingdom	Pertussis	No validation of vaccination by medical charts
Kemp et al ²⁴	1997	New Zealand	Pertussis	Missing disease-specific data on asthma
Strannegård et al ²⁵	1998	Sweden	BCG	No validation of vaccination by medical charts
Hurwitz and Morgenstern ²⁶	2000	US	Pertussis	No validation of vaccination by medical charts
Pahari et al ²⁷	2002	United Kingdom	BCG	No validation of vaccination by medical charts
McKeever et al ²⁸	2002	United Kingdom	pertussis	Survival-analysis design
Bager et al ²⁹	2003	Denmark	BCG	Older age groups, asthma-definition standard not met
Benke et al ³⁰	2004	Australia	Pertussis, BCG	No validation of vaccination by medical charts
Da Cunha et al ³¹	2004	United Kingdom	BCG	No validation of vaccination by medical charts
Martignon et al ¹¹	2005	France	Pertussis, BCG	No vaccine-specific data, no asthma-specific data
Enriquez et al ³²	2005	US	Pertussis, BCG	No validation of vaccination by medical charts
García-Marcos ¹⁰	2005	Spain	BCG	No validation of vaccination by medical charts
Bernsen et al ³³	2006	Netherlands	pertussis	No validation of vaccination by medical charts

TABLE 2 Studies Included in the Meta-analysis

Quality Rank (Score)	Trial	Year	Country	Study Design	No. of Children	No. of Unvaccinated Children	Age, y	Potential Confounders Measured
BCG								
1 (6)	Mommers et al ¹⁵	2004	Netherlands, Germany	Nested case control	572	497	7–8	Gender, socioeconomic status, parental smoking, breastfeeding, others
2 (4)	Marks et al ²⁰	2003	Australia	Retrospective	751	442	7–14	Family history of allergy, gender, parental smoking, others
3 (3)	Alm et al ²¹	1997	Sweden	Retrospective	574	358	3.1–7.2	Family history of allergy, parental smoking, gender, breastfeeding, low birth weight, others
4 (3)	Grüber et al ¹⁹	2002	Germany	Prospective	38 808	18 425	6	Gender, others
5 (1)	Grüber et al ²³	2001	Germany	Retrospective	774	682	7	Family history of allergy, gender, breastfeeding, others
Pertussis								
1 (9)	Farooqi and Hopkin ¹⁴	1998	United Kingdom	Retrospective	1934	498	12–16	Family history of allergy, gender, birth weight, breastfeeding, parental smoking, socioeconomic status, others
2 (8)	Nilsson ¹³	2003	Sweden	Randomized, controlled trial	490	177	7	Family history of allergy, gender, parental smoking, others
3 (6)	Mommers et al ¹⁵	2004	Netherlands, Germany	Nested case control	572	208	7–8	Gender, socioeconomic status, parental smoking, breastfeeding, others
4 (5)	Bernsen et al ¹⁶	2003	Netherlands	Retrospective	1724	44	6	Birth order, allergy in father, family size, year of birth, maternal age
5 (4)	Maitra et al ¹⁷	2004	United Kingdom	Prospective	13 810	340	5.75–6.75	Family history of allergy, parental smoking, others
6 (3)	DeStefano et al ¹⁸	2002	United States	Prospective	167 240	6069	1.5–6.0	Gender, birth weight, socioeconomic status, others
7 (1)	Grüber et al ²²	2003	Germany	Prospective	893	527	5	Family history of allergy, socioeconomic status

analyses including only the 3 or 4 studies with the highest methodologic quality. No difference was noted in either the heterogeneity between studies or the overall measure.

Pertussis Vaccination and Asthma

Figure 2 presents the ORs and 95% CIs of the 7 studies on pertussis vaccination and asthma. Two studies reported that vaccination induced asthma,^{14,17} but in only 1 of them did the between-group difference reach statistical significance.¹⁴ The heterogeneity of the 7 studies was found to be statistically significant ($\chi^2 = 13.98$; $P = .03$); therefore, the OR was calculated according to the random-effect model to determine the overall estimate. The OR was 0.99 (95% CI: 0.78–1.25), which indicates that pertussis vaccination had no detectable adverse effect on asthma. Additional calculations using the fixed-effect model yielded similar results (OR: 1.02 [95% CI: 0.92–1.13]).

Because the heterogeneity consistently reached statistical significance with exclusion of each of the studies, we continued to use the random-effect model for our sensitivity analysis. The results remained similar after exclusion of each study, with an OR of 0.93 to 1.1 and a CI that overlapped 1.0 in all analyses. Table 3 summarizes these results, as well as an additional 2 sensitivity analyses including only the 6 studies with the highest-quality scores. There was no change in heterogeneity or in the overall measure. Including only the 5 studies with the highest-quality scores reduced the heterogeneity below the level of significance ($\chi^2 = 6.62$; $P = .157$). In this case, when we used the fixed-effect model, pertussis vaccination had a borderline significant provocative effect on asthma in childhood (OR: 1.26 [95% CI: 1.04–1.54]).

DISCUSSION

This meta-analysis was conducted to clarify the controversial findings for the association of immunization and

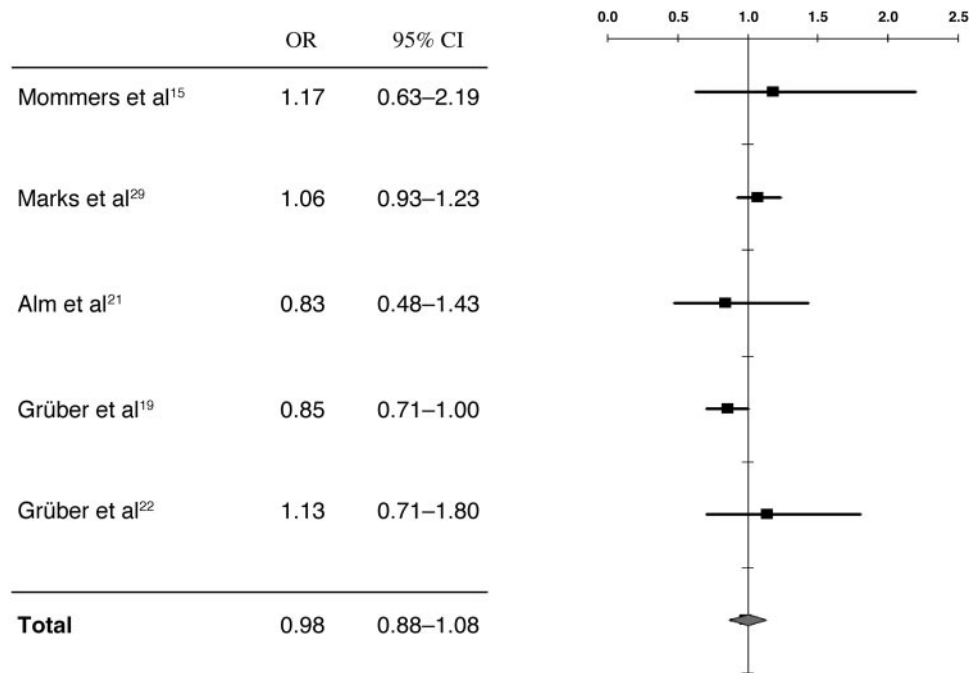


FIGURE 1
ORs for the association of asthma with BCG vaccination in 5 studies. The horizontal bars represent the 95% CIs.

TABLE 3 Sensitivity Analyses for Meta-analysis ORs

Studies (Quality Rank)	Heterogeneity			Precision-Based Estimated OR (95% CI)	DerSimonian and Laird-Based OR (95% CI)
	χ^2	Degrees of Freedom	<i>P</i>		
BCG vaccination and asthma					
All studies (1–5) ^a	4.89	4	.299	0.98 (0.88–1.08)	—
Highest quality (1–4) ^a	4.49	3	.213	0.97 (0.87–1.08)	—
Highest quality (1–3) ^a	0.85	2	.655	1.05 (0.92–1.20)	—
Pertussis vaccination and asthma					
All studies (1–7)	13.98	6	.03	1.02 (0.92–1.13)	0.99 (0.78–1.25)
Highest quality (1–6)	11.76	6	.038	1.04 (0.94–1.16)	1.04 (0.80–1.35)
Highest quality (1–5) ^a	6.62	4	.157	1.26 (1.04–1.54)	—
Small unvaccinated cohorts excluded (1–3 and 7)	9.07	3	.028	1.18 (0.98–1.43)	0.98 (0.63–1.51)

^a The DerSimonian and Laird test was not performed because statistically significant heterogeneity was not observed.

risk of atopy. Some vaccines were implicated as having an inciting effect (most notably whole-cell pertussis vaccine but also measles-mumps-rubella vaccine), whereas others were suggested to have a protective effect (most notably BCG vaccine). To cope with the suboptimal methodologies and the multiple outcomes, we selected a single outcome (asthma), excluded the studies with a cross-sectional design, and included only studies that adhered to standard methods of validation of exposure and predetermined outcome criteria. We also focused only on the 2 most-studied vaccines in this context. Although neither vaccine is used as widely today as it was a decade ago, the BCG vaccine was routinely administered to all children in the United Kingdom and Finland until recently and is still universally used in

France,³⁸ and the DTP (rather than the diphtheria-tetanus-acellular pertussis [DTaP]) vaccines are still widely used outside Europe and North America.³⁹

Our final selection comprised 11 studies that included a total of 227 570 subjects (1 of which assessed both vaccines). The results did not support either a protective or provocative effect of BCG or whole-cell pertussis vaccination in the first year of life on the likelihood of acquiring asthma in childhood and adolescence.

In the past 3 decades we have witnessed a spectacular increase in the prevalence of asthma and allergic disease worldwide: >130 million people suffer from asthma, and the numbers are increasing.⁴⁰ This quadruple increase is most notable in countries with a Western lifestyle. A critical role for environmental factors in driving

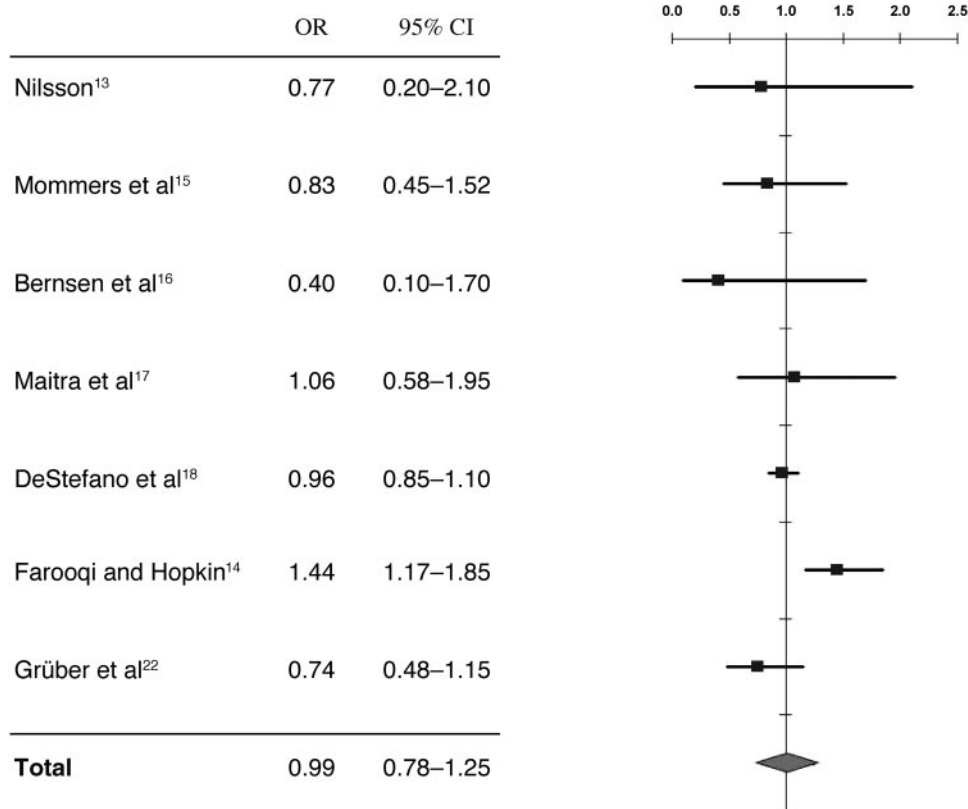


FIGURE 2

ORs for the association of asthma with whole-cell pertussis vaccination in 7 studies. The horizontal bars represent the 95% CIs.

the expression of asthma and other allergic diseases is considered almost certain.¹ Exposure to high amounts of allergens, such as those derived from house dust mites, cannot explain the large intercountry differences in asthma rates or the rising trends. Concerns have been raised that factors that once provided protection from allergic disease may have been lost from the environment.

In 1989, Strachan⁷ proposed the hygiene hypothesis, which claims that the apparent rise in the prevalence of allergic disease “could be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally.” This hypothesis suggested that modern-day cleanliness has decreased microorganism stimulation of the immune system in infants, leading to the persistence of an immature immune response and, consequently, an imbalance in T-helper 1 (Th1) and Th2 immunity, which may lead to atopy. Persistence of the immature immune response may depend on the presence of certain predisposing genes and specific environmental exposures.

More recently, extensive epidemiologic research has shown that exposure to microorganisms or their products may play a role in allergic disease. Indirect support was provided by findings of a considerably lower prevalence

of allergic diseases in developing countries and in rural areas within 1 country.⁴¹ The overrepresentation of allergic sensitization in firstborn children and the lower rates in children from large families or attending day care also point to a possible protective effect of a frequent exchange of infections.⁴⁰ Accordingly, exposure to microbial substances in stables and in unpasteurized (raw) milk was found to be inversely related to the development of atopy, and the endotoxin load in the mattresses of children brought up in a rural environment was inversely related to the occurrence of hay fever and grass sensitization.⁴²

The hygiene hypothesis implies that any interventional factor that reduces childhood infections may potentially be associated with an increased incidence of allergic diseases. Several studies have demonstrated a statistically significant^{14,24,26} or nonsignificant²² tendency toward a higher risk of atopy in individuals who have been immunized with the whole-cell pertussis vaccine, administered in most cases as a component of the DTP vaccine. Of these 3 components, pertussis toxin was shown to cause an increased production of pertussis-specific immunoglobulin E antibodies in both animal and human models. However, in most cases, this was a transient change that was unrelated to the development of atopic conditions.¹⁹ In this analysis we were not able

to differentiate the individual effect of the diphtheria and tetanus components on the measured outcomes.

Our finding from this analysis that pertussis vaccination is not related to asthma incidence is in keeping with the only randomized, controlled trial to date that addressed this issue. Nilsson et al¹³ randomly assigned 667 Swedish children to 4 groups to receive 2- or 5-component acellular pertussis vaccine, whole-cell pertussis vaccine, or DPT vaccine. The cumulative incidence of asthma at 7 years was similar in all groups after adjustment for family history of atopic disease, environmental smoking at home, and other living conditions. Similar findings were noted in other nonrandomized well-controlled studies that compared pertussis-vaccinated and unvaccinated children. One large-scale ecological study even reported a negative correlation of pertussis immunization and wheezing at the population level.⁴³

The selection process and sensitivity analyses used in this study were designed to address several of the methodologic challenges associated with nonrandomized observational studies of vaccinated and unvaccinated populations. To reduce the effect of recall bias, we excluded 9 studies from researchers who failed to validate vaccination status with medical charts. In addition, the unique attributes of specific unvaccinated subpopulations may also act as confounders or introduce misclassification. For example, parents who elect not to vaccinate their child may practice a naturalistic lifestyle, thus introducing various confounding factors. They may also be less likely to seek medical assistance in events of wheezing/asthma and, therefore, will be underrepresented in studies that use only medical charts to assess outcome. McKeever et al²⁸ found that nonvaccinated children visited their general practitioner less often than vaccinated children in the same cohort, and the association between vaccination and asthma varied considerably between the subgroups according to their visit frequency. Therefore, we performed a separate analysis of studies in which the unvaccinated children comprised >25% of the study cohort, because nonvaccination in these cases may not have been limited to secluded individuals. Alternatively, the differences in beliefs and lifestyle of this subgroup and the vaccinated population may not have been as profound as expected. We found that the results of this subgroup analysis were in keeping with the others in our study.

The only borderline significant positive association of vaccination with asthma incidence was noted in the analysis of the 5 studies of the highest methodologic quality score. The results showed that pertussis vaccine had a provocative effect on the occurrence of asthma (OR: 1.26 [95% CI: 1.04–1.54]). This finding highlights the importance of performing additional, adequately designed evidence-based studies.

BCG immunization during infancy has been suggested to protect against atopic diseases and asthma.

Unlike the pertussis vaccine, BCG immunization involves the inoculation of live mycobacteria. Therefore, it may have a direct effect on the immune system, similar to that of tuberculosis and other bacterial infections, and provide protection against atopy in accordance with the hygiene theory. In animal models, BCG vaccination has resulted in a preferential proliferation of Th1 cells and inhibited subsequent immunoglobulin E antibody formation and allergen-induced airway inflammation, even in the presence of established allergies.^{44–48} This protective effect was also suggested in several human studies, although in most cases, it did not reach statistical significance. One exception is the large-scale study of Grüber et al,¹⁹ who compared German and Dutch children and demonstrated a moderate (and borderline significant) protective effect of BCG vaccination on childhood asthma.

The results of our meta-analysis do not support these earlier findings. Similar to pertussis, we found no statistically significant association between BCG vaccination and subsequent asthma/wheezing in childhood and adolescence.

It is noteworthy that much of the preliminary evidence of such a protective impact was reported in studies that used the response to purified protein derivative as a surrogate marker for successful BCG inoculation.^{49,50} We did not include them in our analysis, because it is unclear if the decreased tuberculin responses were induced by atopy or if they contributed to the atopy-related Th2-type immune response. In another study in Spanish schoolchildren, which suggested a weak but significant protective effect of BCG immunization against asthma and hay fever, the BCG vaccination status was not validated against the medical charts.¹⁰ Nevertheless, we included it in our analysis because the authors, who were aware of the problem, claimed that the effect of this potential misclassification was nondifferential, so that the statistically significant increase in the calculated risk was probably an underestimate. In view of this rationale, we also performed an analysis including this study, and the overall protective effect of BCG vaccination neared but did not reach statistical significance.

Thus, the currently available evidence does not indicate a protective effect of BCG vaccination on asthma incidence, although a tendency for such an effect can be detected and may be affirmed in future randomized, controlled trials.

CONCLUSIONS

The currently available data do not support an association, either provocative or protective, of BCG or whole-cell pertussis vaccination in infancy and risk of asthma in childhood and adolescence. These findings could be used to relieve parental concerns that could otherwise lead to vaccination refusal.

The lack of robustness of the results of the sensitivity

analyses of pertussis vaccination and the multitude of potential biases in studies that have used a birth-cohort design stress the need for additional adequately controlled, large-scale studies.

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